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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/902,634
Filing Date: July 10, 2001
Appellant(s): ASHKENAZI ET AL.

Ginger R. Dreger
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 30, 2006 appealing from the Office action mailed August 29, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/907,824, containing claims to PRO266 nucleic acids; and

09/904,956, containing claims to PRO266 polypeptides.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Skolnick et al., 2000, TIBTECH, Vol. 18, , pp. 34-39. et al. ;

Bork et al., 1998, Current opinion in Structural Biology, Vol. 8, pp. 331-332;

Opdenakker et al., 2002, Verh. K. Acad. Geneeskd. Belg., 64, pp. 105-136;

Falcone et al., Curr. Opin. Immunol., 1999, 11, pp.670-676.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 39-43 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated protein and an antibody to that protein. The instant application does not disclose a specific biological role for this protein or the antibody that specifically binds to this protein or their significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The DNA of the instant application has been isolated because of its similarity to a known DNA. There is little doubt that, after complete characterization, this protein and an antibody that specifically binds to that

prtoein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to an antibody that binds to a polypeptide of as yet undetermined function or biological significance. It is clear from the instant specification that the instant novel polypeptides, designated PRO266 polypeptides and comprising amino acid sequence of SEQ ID NO: 91, have homology to proteins containing leucine-rich repeats (page 12, first three paragraphs of the instant specification). More specifically, "it is [...] believed that PRO266 polypeptide disclosed in the present application is a newly identified member of the leucine rich repeat family and possesses ligand-binding activity and neuronal development typical of this family. SLIT has been

shown to be useful in the study and treatment of Alzheimer's disease, supra, and thus, PRO266 may have involvement in the study and cure of this disease " (page 102, last two lines and page 103, lines 1-3). Thus, based on the structural similarities to different known proteins with known or proposed function, it has been suggested that the PRO266 of the instant invention would also possess similar biological activity. Numerous publications exist on a topic of predicting protein functions from structural similarities or homology to the known proteins. It is well described in the art that amino acid structure cannot necessarily predict the function of the protein: "Knowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (see Skolnick et al., Box 2 on page 36 and the whole paper). Moreover, "Structural similarity does not necessarily mean a common evolutionary origin and homologous sequences may evolve into different folds (according to current classification schemes) (See Bork et al., Current Opinion in structural Biology, 1998, 8, page 332, first column, second paragraph). Thus, according to the state of the art, functional characteristics of a protein cannot be unequivocally extrapolated from its structural characteristics. Because the various members of the family of proteins containing leucine-rich repeats have diverse and different biological activity, including protein-protein interactions and neuronal development (page 12, third paragraph), one cannot predict that a protein of the instant invention will possess any particular activity based solely upon its structural similarity to the SLIT protein from Drosophilae, a member of this family.

In the absence of knowledge of the biological significance of this specific polypeptide, there is no immediately obvious patentable use for the antibody that binds to

it. The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the instant polypeptide is associated with any diseases or disorder, including Alzheimer's disease, as asserted in the instant specification (page 103, line 2). Examples 74 and 77 of the instant specification (pages 208-209 and 210, respectively), which present information about the ability of PRO266 to stimulate the proliferation of stimulated T-lymphocytes and induce inflammation in skin vascular permeability assay fail to provide sound scientific reasoning as how these data lead to the assertion of specific and substantial utility of the claimed anti-PRO266 antibodies in stimulation or inhibition of "an immune response [...] where stimulation of an immune response is beneficial" (p.210, lines 25-26) or with respect to treatment of Alzheimer's disease. Based on analysis of the presented data and knowledge in the art, a skilled artisan would not have reasonable expectations that, for example, administration of anti-PRO266 antibodies would have any effect beneficial to an Alzheimer's disease patient.

Further, to employ the anti-PRO266 antibodies of the instant invention "in diagnostic assays for PRO, e.g., detecting its expression in specific cells, tissues, or serum", as suggested in the instant specification (page 146, lines 33-34) is not a "real world" because it would eventually relate to a protein for which no biological function is known. The instant application also fails to demonstrate use of the antibodies as markers for any disease or condition (which would be a real world use). Because the instant specification does not teach a biological activity of the protein, one cannot prevent or treat a condition or disease as implied by the specification by delivering anti-PRO266 antibodies formulated as immunoliposomes (page 145-146, sections 8 and 9). . To

employ the claimed antibody of the instant invention in any of the disclosed methods would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the claimed antibody, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(10) Response to Argument

Issue I: Utility under 35 U.S.C. § 101

At pages 4-6 of the Brief, Appellant presents a summary of the arguments to support the patentable utility of the claimed anti-PRO266 antibodies, which are asserted to be useful "in the treatment of conditions where inflammation may lead to tissue destruction, like in autoimmune diseases, for instance" (top at page 5). Specifically Appellant argues that "asserted patentable utility for the claimed antibodies to PRO266

polypeptides is based upon the positive data for PRO266 in the Skin Vascular Permeability (SVP) assay (Assay 64, Example 77, page 210, lines 22-38). [...] The SVP assay is a well-established assay for evaluating test compounds for their ability to induce inflammation" (bottom at page 4). Appellant further refers to the Declaration of Sherman Fong and publications of Opdenakker et al. and Falcone et al. and states that these documents supports Appellant's statement that proinflammatory molecules are useful in treating a variety of inflammatory disease conditions (middle at page 5 of the Brief). Appellant's arguments have been fully considered but are not persuasive for the following reasons.

From the information presented within Example 77 (Assay 64, page 210 of the instant specification) it is evident that intradermal injection of PRO266 polypeptides caused infiltration of inflammatory cell into the skin of guinea pigs. Thus, it appears that the instant PRO266 protein is generally associated with inflammation, which is the most common and perhaps one the evolutionary oldest physiological reaction of an organism to an entry of a "foreign" protein. However, the instant specification fails to provide any evidence or scientific reasoning that the results of Example 77 would support a conclusion that PRO266 is specifically associated with any specific particular inflammatory disease or condition, including cancer, infection or autoimmune disease. Moreover, there appears to be total lack of evidence that an antibody to a protein that tests positive in SVP assay is immediately useful "in the treatment of conditions where inflammation may lead to tissue destruction" (middle at page 5) as argued by Appellant. The Examiner maintains the position that finding of a positive testing of PRO266 polypeptides in SVP assay is, at the most, a motivating invitation for further research,

experimentation and confirmation as to whether PRO266 and, consequently anti-PRO266 antibodies, are useful for treatment of a pathological condition. However, 35 USC § 101 clearly states that the invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention.

The Court in *Brenner v. Manson* held that "[t]he basic *pro quid quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point – where specific benefit exists in currently available form – there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695.

§101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. *Brenner's* standard has been interpreted to mean that "vague, general disclosures or arguments of "useful in research" or "useful as building blocks of value to the researcher" would not satisfy §101. See *Kirk*, 376 F. 2d at 945 153 USPQ at 55 (interpreting *Brenner*).

Characterization of the instant PRO266 polypeptides as capable to induce an inflammation in mammalian skin is clearly not sufficient to establish their specific significance and substantiate utility of anti-PRO266 antibodies. The Examiner never disputed that the instant claimed PRO266 protein could belong to the family of proinflammatory molecules. However, in the absence of the biological significance of these particular PRO266 molecules or their relevance to a particular physiological process or pathological condition, the information that PRO266 proteins cause local inflammation when injected to the skin does not provide for their specific, substantial and

credible utility. Thus, the record does not support Appellant's position that the characterization of a protein that tests positive in SVP assay would have suggested a specific biological function, or any other basis for patentable utility, to a person skilled in the art at the time the application was filed. In the terms used by the *Brenner* Court, such a characterization does not provide a specific utility in currently available form.

At pages 7-11 of the Brief, Appellant traverses the rejection first reviewing the decisions in *Brenner v. Manson, Nelson v. Bowler, Cross v. Iizuka.* Appellant further refers to the Utility Examination Guidelines, appropriate section of MPEP pertained to the utility issues and argues that "an Appellant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101" (*In re Langer* and *In re Jolles,* top at p.8). Appellant's review of the issue of utility, the case law that has been cited and the holding that is found in that case law is not disputed. The only point of disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Specifically, Appellant submits that "the data [...] for PRO266, and the extensive knowledge available in the art at the time of present filing on proinflammatory molecules like cytokines, for instance, provide sufficient knowledge on the importance of proinflammatory molecules in combating diseases like cancer or autoimmune diseases, and therefore enable one skilled in the art to make and use the present invention for the treatment of diseases where proinflammatory molecules are useful, like cancer or autoimmune diseases" (bottom at p.11 continuing to p.12). However, as fully explained by the Examiner in the office actions of record, there appears to be no indication within the instant specification or available art of record that a polypeptide, which tests positive

in SVP assay, could be instantly recognizes as a proinflammatory molecule immediately available for practical use in the treatment of any or all of inflammation-related pathologies. The instant specification asserts the use of the instant anti-PRO266 antibodies "to reduce inflammation" (page 6 of the Brief); however, the record does not support this asserted use as a specific and substantial. For example, it is well described in the art that proinflammatory proteins ("molecules") are known to play a key role in the migration of inflammatory cells in autoimmune diseases and in invasive cancers (see Opdenakker et al, 2002, Verh. K. Acad. Geneeskd Belg., 64 (2), pp. 105-36, page 123, Summary). It is also recognized in the art that the spectrum of action of proinflammatory molecules is very broad and also dependent on the timing and level of production of a specific proinflammatory protein. Falcone et al. publication (Falcone et al., 1999, Curr. Opin. Immunol., 11 (6), pp. 670-6) discloses, for example, that TNF, a proinflammatory cytokine, can have anti-inflammatory and protective effects against T-cell mediated autoimmunity (page 671, first column); or that "IL-12 is another proinflammatory cytokine, critical for inducing Th1 differentiation, that has also downmodulated inflammatory autoimmune responses" (page 671, second column). It is concluded in review article by Falcone et al. that "cytokines may have completely contradictory roles according to the time they enter the scene in the process of T-cell-mediated autoimmunity. In addition, cytokines may play an unexpected role in autoimmunity by modulating cellular populations other than T cells" (page 672, first column). Thus, the art acknowledges the broad range and complexity of functions of proinflammatory proteins and, therefore, the specific function of a particular molecule cannot be predicted based solely on the notion that it belongs to a family of proinflammatory proteins.

Appellant submits at pp. 12-13 of the Brief, that "the Examiner is applying a heightened standard in this rejection by requiring a showing that "the invention is useful to destroy tumor cells, or to treat any or all of autoimmune diseases", which is improper", and further that "there should be no issue regarding the PRO266 polypeptide as a proinflammatory molecule based on positive [the] results of the SVP assay". However, Appellant mischaracterizes the Examiner's position. It is clear from the instant specification that PRO266 polypeptides "have homology to the proteins of the leucine rich repeat superfamily" (page 3 of the Brief), which supported the originally asserted utility of PRO266 molecules as being useful to treat and cure Alzheimer's disease (see page 102, last two lines and page 103, lines 1-3 of the instant specification). The Examiner never argued structural similarly or homology of the instant PRO266 and members of the subfamily of proinflammatory molecules, as this subfamily comprises a wide variety of structurally unrelated molecules. Appellant's asserted utility of anti-PRO266 antibodies is based on positive results of PRO266 polypeptide test in SVP assay, "therefore a positive result in this SVP assay provides strong evidence for a function for that molecule as a proinflammatory molecule" (middle at page 11 of the Brief). As such, Appellant contends that the PRO266 molecules are members of proinflammatory subfamily of cytokines and that defines their practical utility. The Examiner disagrees that "the results of the SVP assay, which identified pharmacological activity for PRO266, suffices to provide utility in itself" (p.13) because no specific pharmacological activity for PRO266 has been identified, and maintains that the positive results of PRO266 in SVP tests do not provide for immediate use of anti-PRO266 antibodies. 35 U.S.C. §101 requires a utility that is specific and substantial, which means that it provides a specific

benefit in currently available form. The instant specification discloses a structure of a novel PRO266 molecule and asserts its function as a proinflammatory cytokine. The specification provides no meaningful guidance on how such information would allow those skilled in the art to use the claimed anti-PRO266 antibodies in a specific substantial way. Appellant claims a product asserted to be useful as an anti-inflammatory molecule but the specification does not disclose how to interpret those data because the only disclosed information is limited to assertion that anti-PRO266 antibodies potentially block a novel proinflammatory molecule of unknown function. Just as the process claimed in *Brenner* lacked utility because the specification did not disclose how to use the end-product, the product claims here lack utility, based on their use, e.g. as anti- or proinflammatory molecules, because the specification does not disclose how to use the antibodies that bind PRO266 polypeptides.

Appellant's reference to *Nelson v. Bowler* appears to be misplaced (pages 13-14 of the Brief). The fact pattern in *Nelson* is not analogous to this case; in the instant case Appellant has not provided evidence of pharmacological utility, either *in vivo* or *in vitro*. Therefore, contrary to Appellant's statement, because of the absence of factual evidence of identification of pharmacological activity for PRO266, there appears to be no support of practical utility either.

At pages 14-15 of the Brief, Appellant traverses the rejection on the premises that "proinflammatory molecules play a primary role in the pathology of many diseases and also [that there is a] a nexus between proinflammation and the treatment of a variety of inflammatory disease conditions like tumorigenesis, generalized inflammation, diabetic retinopathy, autoimmune conditions, etc." and refers to Declaration of Sherman Fong

(also at p.5). Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

The Examiner maintains the position that because at the time of filing no specific biological significance or association with a specific clinical or physiological condition was disclosed for the PRO266 polypeptides, which defines the practical utility of the instant anti-PRO266 antibodies, then Applicant's invention is incomplete for failing to meet 35 U.S.C. § 101 requirement, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. To grant Applicant a patent encompassing an isolated antibody to a naturally occurring human protein, which is not readily usable in it's current form, would be to grant Applicant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" *Brenner v. Manson, Ibid*). To grant Applicant a patent on the claimed anti-PRO266 antibodies based solely upon an assertion that PRO266 polypeptide potentially belongs to a family of proinflammatory molecules is clearly prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted.

The Declaration of Fong under 37 CFR 1.132 filed on October 04, 2004 has been fully considered but is insufficient to overcome the rejection of claims 39-43 based upon 35 U.S.C. 101 for the reasons fully explained earlier and reasons that follow.

At section 7 of the Declaration, Dr. Fong presents a view of a role of proinflammatory molecules with respect to vascular permeability and explains possible events that occur at the site of injury or infection. At section 8, it is further stated that

"proinflammatory molecules are useful in treating infections" because of their ability to stimulate immune cells; that some proinflammatory molecules may cause tissue destruction; and that proinflammatory molecules can be useful in reducing tumor growth because of their ability to inhibit neovascularization. Sections 9-12 describe the Skin Vascular Permeability Assay and its use in studies applying different factors, including growth factors.

There appears to be no disagreement on the role of proinflammatory molecules as presented in the Declaration of Fong and the view existing in the art. At section 13 of the Declaration, Dr. Fong repeats the description of the experiments as disclosed in Examples 74 and 77 on pages 208-210 of the instant specification and further states "that the PRO polypeptide that shows activity in the Skin Vascular permeability assay has specific, substantial and credible utilities. [...] Examples of utilities include, enhancing immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases such as psoriasis" (section 14 of the Declaration). However, the instant specification, as filed, clearly fails to provide any evidence that the instant PRO266 polypeptides are specifically associated with any specific pathological condition, including injury, infection, autoimmune disease or psoriasis. There appears to be no evidence of record presented in the Declaration or recited in the art that would allow a conclusion that positive testing in SVP assay is predictive of immediate use of the testing substance in "enhancing immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases such as psoriasis". In view of lack of this critical information, the Declaration appears to be limited to Dr. Fong's own conclusions and lacking references to scientific reasoning or any evidentiary clinical support (see *Meitzner v. Mindick,* 549

F.2d. 775, 782, 193 USPQ 17, 22 (CCPA 1977), "Argument of counsel cannot take the place of evidence lacking in the record").

The Examiner never argued that proinflammatory molecules play important and diverse roles in pathology of inflammation in general; however, in view of art recognition of broad range of functions of proinflammatory molecules, the disclosure that the instant PRO266 molecules displayed proinflammatory features in Skin Vascular Permeability Assay does not render the asserted utility of the claimed antibodies to PRO266 polypeptides specific, since the specification does not establish that PRO266 proteins are specifically associated with a particular immune condition, such as a specific autoimmune disease or, for example, psoriasis. It is a matter of law that the claimed invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention. In the instant case, significant further research would have to be conducted to identify diseases, which could be treated by administration of anti-PRO 266 antibodies. Therefore, this asserted utility is not specific and it is not substantial.

The Examiner maintains that because the instant specification does not disclose a credible "real world" use for the claimed antibodies, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

ISSUE II: ***35 USC § 112, enablement***

Claims 39-43 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well

established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

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